

Can early oral prolonged-release oxycodone, with or without naloxone reduce the duration of epidural analgesia after cystectomy? A three-arm, randomized, double-blind, placebo-controlled trial

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Abstract:

Thoracic epidural analgesia (TEA) enhances recovery after bowel surgery. Early postoperative prolonged-release oral formulation of oxycodone or oxycodone/naloxone is potentially useful as a second analgesic step to reduce the duration of TEA. We hypothesized that oxycodone would decrease the duration of TEA and combined with naloxone preserve gastrointestinal function. Ninety patients undergoing open cystectomy and urinary diversion were enrolled in this randomized double-blind, three-arm, parallel-group, placebo-controlled single-center trial between September 2015 and February 2017. Exclusion criteria were known allergy to oxycodone/naloxone, pulmonary diseases, hepatopathy, analgesics non-naïve patients. From postoperative day 3, patients received batches with oxycodone, oxycodone/naloxone or placebo every 12h (n=30 in each arm). Reduction of the epidural drug infusion rate was attempted with the goal to maintain a pain intensity <3 at rest and <5 (numeric rating score) at mobilization during 6h. Primary endpoint was duration of TEA and secondary endpoint return of gastrointestinal function. The median duration of TEA did not differ between patients treated with oxycodone/naloxone (6.7 [range 3.1-10.3] days), oxycodone (7.0 [3.0-9.1]) or placebo (6.4 [3.1-8.4]); $P=0.88$. Time to first defecation was prolonged in the oxycodone group compared to the placebo group (difference 22.48 hours ± 8.95 ; $P=0.037$). In the oxycodone group, we found 8/30 patients with ileus (27%) compared to 2/28 (7%) in the oxycodone/naloxone group and to 2/30 (7%) in the placebo group; ($P=0.031$). Oxycodone, with or without naloxone, did not reduce the duration of TEA. Oxycodone alone led to a delayed return of bowel function, whereas the combination was not different from placebo.

Keywords: pain, oxycodone, oxycodone-naloxone, thoracic epidural analgesia, bowel function

Introduction

Cystectomy combined with urinary diversion is a major abdominal surgery, which is associated with a high incidence of postoperative complications (approximately 60%).^[34] Gastrointestinal complications are frequent (12-25%)^[34] and perioperative techniques aiming at an early return of bowel function are to be pursued.

Optimal postoperative pain management is one of the key factors promoting enhanced recovery after surgery (ERAS). The perioperative use of thoracic epidural analgesia (TEA) for major abdominal surgery is established, not only because of its excellent analgesic properties,^[5] but also because TEA reduces the postoperative stress response, accelerates the return of bowel function,^[20; 42] and may lower postoperative morbidity and mortality.^[1; 16; 21; 30] Once successfully established, TEA is not without limitations and requires constant attention often from an acute pain service to achieve and maintain optimal analgesia. Attention must also be directed to limiting or avoiding side-effects such as hypotension, orthostatic disturbances or motor block, which will reduce the benefits of the technique by preventing the patient from being effectively mobilized after surgery.^[18; 39] In addition, each supplemental day with an indwelling TEA catheter increases the risk of infection,^[19] which is associated with a high morbidity. Therefore, it is important to develop strategies that reduce the duration of TEA

without impairing the benefits. ERAS protocols recommend removing the TEA catheter 48 to 72 hours after surgery, which should not impair the return of the gastrointestinal function.[3] While this approach is well established for colorectal surgery, there is less evidence for small bowel surgery or cystectomy with urinary diversion. In addition, the perioperative administration of non-steroid anti-inflammatory drugs, as usually recommended in the frame of ERAS programs, is of limited use in cystectomy patient as around 75% of these patients have impaired renal function.

In theory, systemic analgesics like oxycodone or combined drug mixtures like oxycodone/naloxone could be a valuable option as a second analgesic step, allowing earlier removal of the epidural catheter without impairing return of the bowel function.[12; 14; 23] The rationale for the combination of oxycodone with naloxone is reduced opioid-induced bowel dysfunction, compared with oxycodone alone.[13; 23] However, evidence is scarce concerning the benefit of early oral administration of opioids after major abdominal surgery involving small bowel resection and anastomosis before return of bowel function.

The objectives of this study in patients undergoing cystectomy and urinary diversion were: 1) to evaluate the effect of oral oxycodone (with and without naloxone), compared to placebo, on duration of TEA (primary endpoint), changes in epidural mixture rate, total amount of epidurally-administered drugs, and amount of systemic administered rescue analgesics; 2) to evaluate the effect of the addition of naloxone to oxycodone on the return of gastrointestinal function (first flatus, first defecation, incidence of constipation and postoperative ileus, postoperative nausea and vomiting). We expected: 1) equal analgesia with a reduced duration of TEA with oxycodone

(w or w/h naloxone), compared to placebo; 2) faster return of bowel function with the combination of oxycodone with naloxone, compared to oxycodone alone.

Methods:

Ethics:

The study was approved by the Ethics Committee of the Canton Bern, Switzerland (Kantonale Ethikkommission Bern, Prof Seiler, KEKBE 068/2015), and by the Swiss Agency for Therapeutic Products (2015DR4112). It was prospectively registered at ClinicalTrials.gov (NCT02516059; principal investigator: P.Y. Wuethrich, M.D.; date of registration: August 3, 2015) and conducted in compliance with the Declaration of Helsinki and Good Clinical Practice. All patients gave written informed consent before participating in the trial.

Study design, inclusion and exclusion criteria:

This was an investigator-initiated, prospective, randomized, double-blinded, double-dummy, three-arm, parallel-group, placebo-controlled, interventional superiority trial conducted at the Department of Urology University Hospital Bern, Switzerland between September 14, 2015 and February 28, 2017. Reporting complied with the recommendations of the Consolidated Standards of Reporting Trials (CONSORT) statements.

Consecutive patients presenting for open cystectomy and urinary diversion (ileal conduit, orthotopic bladder substitute, continent catheterizable ileal reservoir) were screened for eligibility. Participants fulfilling all the following inclusion criteria were eligible for the study:

renal function with an estimated glomerular filtration rate $> 40 \text{ mL} \cdot \text{min}^{-1}$, normal liver function and use of TEA. Exclusion criteria were contra-indications to the class of drugs under study (i.e. known allergy to oxycodone and/or naloxone or other excipients), women who were pregnant or breast feeding (exclusion for surgery per se), known or suspected non-compliance, drug or alcohol abuse, inability to follow the procedures of the study (e.g. due to language problems, dementia and severe psychiatric disorder), severe bronchial asthma, severe chronic obstructive pulmonary disease, severe respiratory depression with hypoxia and/or hypercapnia, moderate to severe hepatic impairment, preoperative use of monoaminoxidase-inhibitors, chronic pain disease, regular use of antiemetics, laxatives, opioids or other types of analgesics, preoperative regular use of non-steroidal anti-inflammatory drugs and steroids.

Blinding and randomization:

Batches and blinding were organized by Mundipharma Medical Company (Basel, Switzerland) and provided by Mundipharma Research GmbH & Co (Cambridge, UK), granting good manufacturing practice. As oxycodone/naloxone tablets were oblong in shape and the oxycodone tablets were round, a double dummy approach was inevitable to warrant the full blinding and the inability to optically recognize the type of drugs administered. One contained only placebo (round and oblong tablets), the second oxycodone (Oxycontin®, Mundipharma Research GmbH & Co Cambridge, UK) plus placebo (oblong tablet) and the third a mixture of oxycodone and naloxone (Targin®; Mundipharma Research GmbH & Co Cambridge, UK) plus placebo (round tablet). The pack for each participant contained enough medication for 5 days: The oxycodone/naloxone arm received 2 tablets of 10 mg / 5 mg (active and placebo) for the first day

followed by 8 tablets of 20 mg / 10 mg for the remaining 4 days. The oxycodone arm received 2 tablets of 10 mg (active and placebo) for the first day followed by 8 tablets of 20 mg for the remaining 4 days. The placebo arm received 2 tablets (one round placebo tablet and one oblong placebo tablet) for the next 5 days. The pack always contained 2 blisters, for example, one containing active oxycodone/naloxone medication and the other containing placebo tablets to blind the supplies.

Study nurses from the Department of Urology delivered the randomized blinded drugs to the intermediate care unit in a sealed package, only labeled with the name of the included patient. This allowed for blinding of the patient, nurses, urologist, pain service personnel, data assessors and statisticians.

Randomization was done by computer-generated list, with blocks of 9 patients; allocation ratio was 1:1:1. Allocation sequence was left in concealed opaque and numbered envelopes. Patients were included strictly according to the lowest number.

Primary and secondary outcomes:

Primary endpoint was the time from start of the epidural analgesia to removal of the epidural catheter (i.e. duration of TEA).

Secondary endpoints were epidural mixture rate (expressed in $\text{mL} \cdot \text{h}^{-1}$), total amount of epidural mixture used per 24 h, every step to reduce the epidural mixture (expressed in differences in epidural mixture rate from day to day, e.g. between postoperative day (POD) 4 vs POD 3, POD 5

vs POD 4 and POD5 vs POD 3), total number of patients per group still with TEA per postoperative day, and use of rescue analgesics (transformed in morphine equivalent). These parameters were recorded daily. We used the numeric rating score (NRS) for pain score assessment, whereby 0 = no pain and 10 = worst pain imaginable. The lowest, highest and average NRS were recorded at rest and during mobilization, which was defined as getting out of bed. NRS score was assessed during TEA checks at least 6 times per day.

Additional secondary endpoints were the incidence of postoperative nausea and vomiting and return of bowel function (first defecation). Patients were actively questioned about nausea and episodes of vomiting were recorded. Documentation including time-points was recorded by dedicated study nurses. First flatus and defecation were recorded similarly. Episodes of constipation and ileus (i.e. delayed return of bowel function) were also recorded. Ileus was defined as postoperative nausea or vomiting associated with abdominal distension requiring cessation of oral intake and intravenous fluid support and/or nasogastric tube placement, or the intolerance of oral intake by POD 5 resulting in patient fasting.[34] Constipation was defined as inability to have a bowel movement by POD 5 with no signs of ileus or small bowel obstruction.[34]

The end of the study was defined as removal of the epidural catheter and return of bowel function.

Standardized perioperative management:

Preoperatively, no antegrade bowel preparation was administered, but two high enemas were given the evening before surgery. Patients had oral intake till midnight before surgery, and were encouraged to drink clear fluid till 2 hours before anesthesia induction.

Standard monitoring included continuous electrocardiographic data, heart rate, nasopharyngeal core temperature, pulse oximetry, invasive mean arterial pressure with a radial artery catheter and central venous pressure with a venous catheter inserted in the right internal jugular vein. An epidural catheter was placed at the T9/T10 level. An 18 gauge epidural needle was inserted by a paramedian approach and the epidural space was identified with the loss-of-resistance technique. After a test dose of 1.5 mL lidocaine 2% with $0.005 \text{ mg} \cdot \text{mL}^{-1}$ epinephrine to rule out subarachnoid or intravascular placement, a 0.25% bupivacaine infusion at a rate of $6\text{--}8 \text{ mL} \cdot \text{h}^{-1}$ was administered. Anesthesia was induced with propofol ($2 \text{ mg} \cdot \text{kg}^{-1}$), fentanyl ($2 \mu\text{g} \cdot \text{kg}^{-1}$) and rocuronium ($0.6 \text{ mg} \cdot \text{kg}^{-1}$), and maintained with isoflurane at an age-corrected minimum alveolar concentration of 0.6. Normothermia was maintained with a convective air warming system (Bair Hugger™, 3M™-Switzerland, Rüschlikon, Switzerland) and using a Hotline® fluid warmer (Smith Medical International Ltd, Ashford, Kent, United Kingdom).

Surgery was performed in a standardized fashion as previously described, with the patient in a 30° head-down position [4; 6; 7]. A gastrostomy tube was placed intraoperatively and the orogastric tube was removed at the end of the procedure. The ureteral stents were exteriorized.

The approach for supporting postoperative gastrointestinal function was standardized and

according to our internal ERAS program guidelines for cystectomy patients. [26] The use of chewing gum was encouraged and clear drinks were allowed the same evening after surgery. Gastrostomy tube was initially left on drainage, and closure of the gastrostomy tube was initiated if no nausea and vomiting was present for > 24 h. Bedside mobilization was encouraged as soon as possible, ideally the same evening after surgery, if not possible not later than the next morning. Gastrointestinal ulcer prophylaxis was done with esomeprazole (for > 48 h). Oral fluids included energy drinks (Resource Senior Active®, Nestlé Health, Switzerland or Ensure®, Abbott Nutrition, Switzerland) on POD 1. The protocol included administration of subcutaneous neostigmine 0.25 to 0.5 mg as prokinetic up to 3 times per day, and peroral laxatives starting on POD 2. Small snacks or mashes were encouraged and introduced on POD 2 but not later than on POD 3. On POD 3, longer mobilization including walking distance and spending time on a chair were encouraged. The gastrostomy tube was removed once the patient had normal stool passage.

Intervention:

The epidural analgesia was activated during closure of the abdominal wall with bupivacaine 1.25 mg*mL⁻¹ (Bupivacaine 0.125% Bioren™, Sintetica-Bioren, Couvet, Switzerland) using a CADD Legacy ambulatory infusion pump (model 6300, Deltec Inc., St Paul, MN). The initial infusion rate was 8 mL*h⁻¹, with a maximum infusion rate of 15 mL*h⁻¹, and with additional bolus doses of 5 mL (lockout time: 1 h) from the end of surgery till 8 am on POD 3. The infusion rate could be adapted if necessary to maintain a NRS < 3 at rest and < 5 during mobilization based on 4 hourly assessments.

Starting from 8 a.m. on POD 3, patients received blinded batches with oxycodone,

oxycodone/naloxone or placebo every 12 h. The oxycodone/naloxone arm received 10 mg / 5 mg for the first day, followed by 20 mg / 10 mg for the remaining 4 days. The oxycodone arm received 10 mg for the first day, followed by 20 mg for the remaining 4 days. On POD 4, attempts to reduce the epidural infusion rate were made in steps of 2 mL to maintain a NRS < 3 at rest and < 5 during mobilization for 6 h. The epidural catheter was removed when a rate of 2 mL*h⁻¹ achieved a NRS < 3 and < 5 at rest and during mobilization for 6 h. If the epidural catheter could not be removed because of regular prophylactic subcutaneous administration of heparin which was always administered at 8 p.m., the epidural infusion was stopped and duration of TEA registered (as removal of the epidural catheter). The catheter was then removed 12 h after the heparin injection according to our guidelines. First rescue medication for breakthrough pain episodes was additional epidural boluses of 5 mL, limited to one bolus per hour. In case of persistent pain, orally administered 5 mg of immediate-release oxycodone every 6 hours was allowed as a second rescue medication in the three arms. In all groups, metamizol 1 g intravenously were given in the intermediate care unit and repeated every 6 h until return of bowel function and then orally administered as a supplement for postoperative analgesia.

Statistics:

Considering the primary objective to compare oxycodone (with and without naloxone) with placebo for the duration of TEA, defining a mean difference of duration of TEA of 1 day as clinically relevant, and expecting a standard deviation of 1 day (based on our internal data), 23 patients per group is the minimum sample size.[32] This was based on the null hypothesis for the proposed study that the duration of TEA was equal across the populations. The criterion for

significance (α) was set at 0.0167 due to the correction for 3 multiple tests (oxycodone/naloxone vs. oxycodone, oxycodone vs. placebo, and oxycodone/naloxone vs. placebo, Bonferroni corrected). The test was 2-tailed. With a sample size of 23 patients per group, the study would have a power of 81.2% to yield a statistically significant result. The computation assumes a common within-group standard deviation of 1. Considering a drop out frequency of a bit more than 20%, 30 patients per group needed to be recruited and a thus total of 90 patients were included. The calculations were made with SamplePower statistical software (v 3.01, IBM, Armonk, New York) and were based on a t-test for independent groups with common variance.

Data were analyzed on a modified intention to treat basis (two patients were excluded after randomization). Data were expressed with means and standard deviations (\pm SD) or medians accompanied with nonparametric 95% confidence intervals (CI) or ranges for continuous variables as appropriate and as frequencies for categorical ones after checking for normality of distribution (Q-Q plots). Categorical data were compared with the chi square test and continuous data by analysis of variance (ANOVA) or Kruskal Wallis (for primary outcome) as appropriate. If ANOVA was significant, Bonferroni correction were applied to account for multiple comparisons. All analyses were performed using STATA statistical software (v 14.0, StataCorp LP, College Station, Texas).

Results:

Of 110 consecutive patients scheduled for open cystectomy and urinary diversion 90 fulfilled the eligibility criteria and were randomized. Of the 90 patients enrolled, 2 patients in the oxycodone/naloxone were excluded because of non-functional TEA after surgery and were excluded from the analysis (Figure 1). Preoperative baseline characteristics were similar among the three groups (Table 1).

Primary endpoint:

The duration of TEA did not differ significantly among the three groups (oxycodone/naloxone: median 6.7 [range 3.1 to 10.3] days, oxycodone: 7.0 [3.0 to 9.1] days or placebo: 6.4 [3.1 to 8.4]; $P=0.880$, (Figure 2).

Secondary endpoints:

The median epidurally administered mixture rate, median total amount of drug administered epidurally, number of boluses administered and the median amount of systemic administered rescue analgesics (morphine equivalent) did not differ significantly among the 3 groups at any time point. A significant reduction of the median epidural mixture rate was achieved in the oxycodone/naloxone (difference 1.41 mL/h [95% CI 0.01-2.73]; $P=0.036$) and in the oxycodone groups (2.17 mL/h [95% CI 0.77-3.57]; $P=0.003$) on POD 4 compared to POD 3 (Table 2). The number of patients who were still under TEA after POD 4 was similar among the groups (on

POD 5: oxycodone/naloxone: 26/28 (93%), oxycodone: 29/30 (97%), placebo: 29/30 (97%); $P=0.727$; on POD 6: oxycodone/naloxone: 20/28 (71%), oxycodone: 23/30 (77%), placebo: 26/30 (87%); $P=0.356$; on POD 7: oxycodone/naloxone: 14/28 (50%), oxycodone: 15/30 (50%), placebo: 15/30 (50%); $P=1.000$; on POD 8: oxycodone/naloxone: 6/28 (21%), oxycodone: 4/30 (13%), placebo: 6/30 (20%); $P=0.691$).

The median average pain scores at rest and during mobilization did not differ significantly between the 3 groups at any time point (Figure 3).

The time in hours to first flatus did not differ significantly among the groups (oxycodone/naloxone mean 48.40 ± 24.48 SD, oxycodone: 42.41 ± 24.16 , placebo: 43.19 hours ± 25.76 ; $P=0.622$). The time in hours to first defecation differed among the groups (oxycodone/naloxone mean 85.91 ± 27.68 SD, oxycodone 97.69 ± 35.70 , placebo: 75.21 hours ± 35.44 ; $P=0.048$). Pairwise comparison showed a significant difference in means between the placebo group and the oxycodone group (22.48 hours ± 8.95 ; $P=0.037$). The difference between the placebo group and the oxycodone/naloxone group and between the oxycodone group and the oxycodone/naloxone group were not statistically significant (10.70 hours ± 9.15 ; $P=0.475$ and 11.78 ± 9.46 ; $P=0.430$, respectively). Delayed return of bowel function significantly differed among the groups (oxycodone/naloxone: 5/28 patients (17%), oxycodone: 14/30 patients (47%), placebo: 7/30 patients (23%); $P=0.027$). In the oxycodone group, we found 8/30 patients with ileus (27%) compared to 2/28 (7%) in the oxycodone/naloxone group and to 2/30 patients in the placebo group (7%) ($P=0.031$).

Episodes of postoperative nausea and vomiting within 48 hours postoperatively were similar

among the groups (POD 1: oxycodone/naloxone: 3/25 (12%), oxycodone 6/24 (17%), placebo 4/26 (15%); $P=0.507$, POD 2: oxycodone/naloxone: 3/25 (12%), oxycodone 6/24 (17%), placebo 3/27 (11%); $P=0.456$).

This study did not demonstrate any significant difference among the groups in regard to other opioid side effects or adverse events such as nausea, vomiting after initiation of administration of the allocated drugs (POD 3: oxycodone/naloxone: 3/25 (12%), oxycodone 4/26 (15%), placebo 4/26 (15%); $P=0.507$; POD 4: oxycodone/naloxone: 3/25 (12%), oxycodone 3/27 (11%), placebo 1/29 (3%); $P=0.804$; POD 5: oxycodone/naloxone: 4/16 (25%), oxycodone 3/20 (15%), placebo 3/23 (13%); $P=0.840$; POD 6: oxycodone/naloxone: 3/17 (18%), oxycodone 6/17 (35%), placebo 4/22 (18%); $P=0.553$; POD 7: oxycodone/naloxone: 2/12 (17%), oxycodone 2/13 (15%), placebo 1/14 (7%); $P=0.777$; POD 8: oxycodone/naloxone: 3/3 (50%), oxycodone 2/2 (50%), placebo 4/2 (67%); $P=0.801$. There were no cases of respiratory depression or strong sedation. There were no cases of TEA catheter associated infections.

Discussion:

The early postoperative oral administration of prolonged-release oxycodone with or without naloxone starting on POD 3 did not reduce the duration of TEA compared to placebo. Pain scores were not affected by the study drugs and all groups had optimal analgesia at rest and during mobilization (mean NRS lower than 3 in all groups at any time points). Most of the secondary endpoints were not different among groups, indirectly confirming that the addition of oxycodone,

with or without naloxone, did not improve pain management. We did however, find a prolonged time to first defecation and a higher incidence of postoperative ileus in patients who received oxycodone alone. As this study failed to demonstrate the superiority of early administration of oxycodone or oxycodone/naloxone alone to reduce the duration of TEA, these results question the practice of early postoperative oral administration of these medications in patients managed with TEA after cystectomy.

The rationale behind the choice of oxycodone was that other at equivalent analgesic dosage μ -opioid agonists, such as fentanyl and morphine, may not be optimal for treating visceral pain. Open cystectomy with urinary diversion is a major abdominopelvic surgery involving extensive mobilization/resection of the peritoneum and a small bowel anastomosis and as such is accompanied by visceral pain. The main mechanism of action for oxycodone is stimulation of the peripheral and central opioid μ and κ receptors. It has been suggested that κ receptors constitute an essential part in the analgesic mechanism of action of oxycodone. Opioid κ receptors may be important for treatment of visceral pain, and hence oxycodone could have a high therapeutic efficacy in this setting.[38; 41]

The rationale behind the oral prolonged-release oxycodone/naloxone formulation is to prevent opioid-induced bowel dysfunction through the local antagonist effect of naloxone in the gut wall, while analgesia is maintained due to the negligible systemic absorption of oral naloxone. Indeed, the bioavailability of oral naloxone is less than 3% as it undergoes extensive first-pass hepatic metabolism. Naloxone binds to μ -opioid receptors on the neurons of the myenteric plexus of the gastrointestinal tract with a higher affinity than oxycodone.[8] Time to first defecation was

slightly longer with prolonged-release oxycodone alone compared to placebo, but not compared to oxycodone/naloxone. As the power calculation of this study was not based on this parameter, we cannot exclude that the non-significance between the placebo group and the oxycodone/naloxone group and between the oxycodone group and the oxycodone/naloxone group might be the result of lack of power. However, these results confirm precedent observations on healthy volunteers showing that prolonged-release oxycodone significantly extended colon arrival time compared to placebo and that the addition of prolonged-release naloxone resulted in similar colon arrival time as placebo.[35] The gastrointestinal effects of oxycodone are complex as both excitatory and inhibitory neural inputs to the gastrointestinal muscle layer can be interrupted. The activation of the μ -opioid receptors on myenteric and submucosal neurons in the lamina propria of the stomach, small and large intestines walls play a major role.[22] On one hand, inhibition of excitatory neural inputs reduce distension-induced peristaltic contraction. On the other hand, the blockade of inhibitory neural inputs increases gastrointestinal muscle activity and resting muscle tone is elevated. This results in delayed/inhibited gastric emptying, increased pyloric muscle tone, delayed transit through the intestines and elevated resting anal sphincter tonus.[8; 22; 28; 37] While the benefit of prolonged-release oral oxycodone/naloxone on constipation has been well established in chronic pain treatment[11; 17; 40] and cancer patients[2], the benefit is less clear in the perioperative setting. In our opinion, this is the first study in which prolonged-release oxycodone with or without naloxone were administered early after major abdominopelvic surgery with small bowel surgery. The literature on postoperative administration of prolonged-release oxycodone with or

without naloxone is scarce and mostly focused on orthopedic joint surgery and minimal-invasive gynecological hysterectomy. [12; 23] If prolonged-release oxycodone with naloxone offers a similar analgesia compared to oxycodone alone with better gastrointestinal function, in the chronic pain patients, these observations are inconclusive in the postoperative setting. An explanation could also be the short period of treatment. Comelon et al. found no benefit of oxycodone/naloxone compared to oxycodone alone in patients undergoing laparoscopic hysterectomy. However, they used oxycodone as a first line analgesic treatment, and no regional technique was used with the exception of bupivacaine injection at the incision sites.[12]

An explanation why prolonged-release oxycodone failed to reduce the duration of TEA could be the specific pharmacokinetic conditions related to the early postoperative setting of a small bowel resection and anastomosis.[31] Indeed, the bioavailability of orally administered oxycodone is high in healthy volunteers, however if this can be projected in these cystectomy patients is questionable.[36] Delayed gastrointestinal recovery is frequent after cystectomy and urinary diversion and is considered an important driver for LOS after cystectomy.[10] The postoperative ileus related increased length of hospital stay may in turn contribute to nosocomial infections and increased readmission rate. In this study, the early oral administration of prolonged-release oxycodone alone increased the time to first defecation compared to placebo, without affecting pain scores or duration of TEA. Therefore, this treatment option cannot be recommended after cystectomy due to the increased risk of postoperative ileus. This is an important consideration as this is in line with the ERAS recommendation to avoid the use of opioids and to implement a multimodal opioid free postoperative analgesia.[15]

This study was powered to determine a difference in duration of TEA. This choice as primary endpoint may be considered as a limitation, given the variability of this measure depending on the patient population. Most randomized clinical trials on analgesic techniques were powered on pain intensity reduction (NRS). However, in this study, the focus was to determine if, after 3 days, systemic administration of prolonged release analgesics is a viable alternative to TEA without impairing the beneficial side effect of TEA. A potential limitation could be postoperative gastroparesis as oxycodone could be liberated in the stomach but not absorbed, thus after return of gastric function a supranormal systemic concentration of the liberated drugs could occur due to the absorption in the small bowel. However, here all patients had a gastrostomy and according to our internal protocol, in case of dysmotility or upper abdominal discomfort, this could be left open, allowing for liberation of gastric content. In addition, this trial was a three-way comparison. This led to multiple significance tests and possibly to misleading *P*-values.

An additional limitation of this study is the relative long duration of TEA compared to other centers, potentially limiting the generalization of our findings. Indeed, most ERAS protocols including rectal/pelvic surgery and the new guidelines of the ERAS society for perioperative care after radical cystectomy do recommend to leave the TEA in place for 48 to 72 hours postoperatively.[9; 29] However, these recommendations are based on low level evidence in cystectomy patients, and the optimal duration of epidural analgesia in terms of patient outcomes and satisfaction is still unclear.[27] Due to the excellent analgesic properties, reduction of surgical stress, minimization of catabolic and inflammatory response, facilitation of recovery of bowel function and enhancement of functional recovery, some institutions prefer to keep the

epidural catheter longer.[15; 33] Noticeably, Lee et al. found a gastrointestinal recovery time (defined as first toleration of food, and first bowel movement) of 5.5 days using alvimopan to accelerate gastrointestinal recovery,[24] and in a previous randomized clinical trial we found that normal bowel function (normal feces) returned at around 6 days after surgery.[25] Because of the variable practice, our results remain applicable to clinical settings using a similar protocol.

Conclusion:

In conclusion, neither early oral administration of prolonged-release oxycodone combined with naloxone, nor oxycodone alone, could reduce the duration of TEA. As the time to first defecation was increased in patients treated with oxycodone alone and the medication conferred no additional benefit in term of analgesia, early postoperative administration of oxycodone cannot be recommended in patients undergoing cystectomy and urinary diversion. Although the addition of naloxone counteracted the negative impact of oxycodone alone on bowel function, the overall effect was not different from placebo. Therefore, also the combination cannot be recommended.

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References

- [1] Ahlers O, Nachtigall I, Lenze J, Goldmann A, Schulte E, Hohne C, Fritz G, Keh D. Intraoperative thoracic epidural anaesthesia attenuates stress-induced immunosuppression in patients undergoing major abdominal surgery. *Br J Anaesth* 2008;101(6):781-787.
- [2] Ahmedzai SH, Nauck F, Bar-Sela G, Bosse B, Leyendecker P, Hopp M. A randomized, double-blind, active-controlled, double-dummy, parallel-group study to determine the safety and efficacy of oxycodone/naloxone prolonged-release tablets in patients with moderate/severe, chronic cancer pain. *Palliat Med* 2012;26(1):50-60.
- [3] Basse L, Hjort Jakobsen D, Billesbølle P, Werner M, Kehlet H. A clinical pathway to accelerate recovery after colonic resection. *Ann Surg* 2000;232(1):51-57.

- [4] Bhatta Dhar N, Kessler TM, Mills RD, Burkhard F, Studer UE. Nerve-sparing radical cystectomy and orthotopic bladder replacement in female patients. *Eur Urol* 2007;52(4):1006-1014.
- [5] Block BM, Liu SS, Rowlingson AJ, Cowan AR, Cowan JA, Jr., Wu CL. Efficacy of postoperative epidural analgesia: a meta-analysis. *Jama* 2003;290(18):2455-2463.
- [6] Burkhard FC, Kessler TM, Mills R, Studer UE. Continent urinary diversion. *Crit Rev Oncol Hematol* 2006;57(3):255-264.
- [7] Burkhard FC, Roth B, Zehnder P, Studer UE. Lymphadenectomy for bladder cancer: indications and controversies. *Urol Clin North Am* 2011;38(4):397-405, v.
- [8] Burness CB, Keating GM. Oxycodone/Naloxone prolonged-release: a review of its use in the management of chronic pain while counteracting opioid-induced constipation. *Drugs* 2014;74(3):353-375.
- [9] Cerantola Y, Valerio M, Persson B, Jichlinski P, Ljungqvist O, Hubner M, Kassouf W, Muller S, Baldini G, Carli F, Naesheim T, Ytrebo L, Revhaug A, Lassen K, Knutsen T, Aarseth E, Wiklund P, Patel HR. Guidelines for perioperative care after radical cystectomy for bladder cancer: Enhanced Recovery After Surgery (ERAS((R))) society recommendations. *Clin Nutr* 2013;32(6):879-887.
- [10] Chang SS, Baumgartner RG, Wells N, Cookson MS, Smith JA, Jr. Causes of increased hospital stay after radical cystectomy in a clinical pathway setting. *J Urol* 2002;167(1):208-211.

- [11] Cloutier C, Taliano J, O'Mahony W, Csanadi M, Cohen G, Sutton I, Sinclair D, Awde M, Henein S, Robinson L, Eisenhoffer J, Piraino PS, Harsanyi Z, Michalko KJ. Controlled-release oxycodone and naloxone in the treatment of chronic low back pain: a placebo-controlled, randomized study. *Pain Res Manag* 2013;18(2):75-82.
- [12] Comelon M, Wisloff-Aase K, Raeder J, Draegni T, Undersrud H, Qvigstad E, Bjerkelund CE, Lenz H. A comparison of oxycodone prolonged-release vs. oxycodone + naloxone prolonged-release after laparoscopic hysterectomy. *Acta Anaesthesiol Scand* 2013;57(4):509-517.
- [13] Creamer F, Balfour A, Nimmo S, Foo I, Norrie JD, Williams LJ, Fearon KC, Paterson HM. Randomized open-label phase II study comparing oxycodone-naloxone with oxycodone in early return of gastrointestinal function after laparoscopic colorectal surgery. *Br J Surg* 2017;104(1):42-51.
- [14] Ding Z, Wang K, Wang B, Zhou N, Li H, Yan B. Efficacy and tolerability of oxycodone versus fentanyl for intravenous patient-controlled analgesia after gastrointestinal laparotomy: A prospective, randomized, double-blind study. *Medicine (Baltimore)* 2016;95(39):e4943.
- [15] Feldheiser A, Aziz O, Baldini G, Cox BP, Fearon KC, Feldman LS, Gan TJ, Kennedy RH, Ljungqvist O, Lobo DN, Miller T, Radtke FF, Ruiz Garces T, Schricker T, Scott MJ, Thacker JK, Ytrebo LM, Carli F. Enhanced Recovery After Surgery (ERAS) for gastrointestinal surgery, part 2: consensus statement for anaesthesia practice. *Acta*

- Anaesthesiol Scand 2016;60(3):289-334.
- [16] Freise H, Van Aken HK. Risks and benefits of thoracic epidural anaesthesia. *Br J Anaesth* 2011;107(6):859-868.
- [17] Gatti A, Casali M, Lazzari M, Tufaro G, Gafforio P, Silvestri C, Marcassa C, Sabato AF. Prolonged-release oxycodone/naloxone in nonmalignant pain: single-center study in patients with constipation. *Adv Ther* 2013;30(1):41-59.
- [18] Gramigni E, Bracco D, Carli F. Epidural analgesia and postoperative orthostatic haemodynamic changes: observational study. *Eur J Anaesthesiol* 2013;30(7):398-404.
- [19] Grewal S, Hocking G, Wildsmith JA. Epidural abscesses. *British journal of anaesthesia* 2006;96(3):292-302.
- [20] Guay J, Nishimori M, Kopp SL. Epidural Local Anesthetics Versus Opioid-Based Analgesic Regimens for Postoperative Gastrointestinal Paralysis, Vomiting, and Pain After Abdominal Surgery: A Cochrane Review. *Anesth Analg* 2016;123(6):1591-1602.
- [21] Gupta A, Bjornsson A, Fredriksson M, Hallbook O, Eintrei C. Reduction in mortality after epidural anaesthesia and analgesia in patients undergoing rectal but not colonic cancer surgery: a retrospective analysis of data from 655 patients in central Sweden. *Br J Anaesth* 2011;107(2):164-170.
- [22] Holzer P. Opioid receptors in the gastrointestinal tract. *Regul Pept* 2009;155(1-3):11-17.
- [23] Kuusniemi K, Zollner J, Sjoval S, Huhtala J, Karjalainen P, Kokki M, Lemken J, Oppermann J, Kokki H. Prolonged-release oxycodone/naloxone in postoperative pain

- management: from a randomized clinical trial to usual clinical practice. *J Int Med Res* 2012;40(5):1775-1793.
- [24] Lee CT, Chang SS, Kamat AM, Amiel G, Beard TL, Fergany A, Karnes RJ, Kurz A, Menon V, Sexton WJ, Slaton JW, Svatek RS, Wilson SS, Techner L, Bihrlle R, Steinberg GD, Koch M. Alvimopan accelerates gastrointestinal recovery after radical cystectomy: a multicenter randomized placebo-controlled trial. *Eur Urol* 2014;66(2):265-272.
- [25] Loffel LM, Burkhard FC, Takala J, Wuethrich PY. Impact of a Potassium-enriched, Chloride-depleted 5% Glucose Solution on Gastrointestinal Function after Major Abdominopelvic Surgery: Results of a Randomized Controlled Trial. *Anesthesiology* 2016;125(4):678-689.
- [26] Loffel LM, Kleeb B, Burkhard FC, Wuethrich PY. Perioperative use of crystalloids in patients undergoing open radical cystectomy: balanced Ringer's maleate versus a glucose 5%/potassium-based balanced solution: study protocol for a randomized controlled trial. *Trials* 2014;15:276.
- [27] Maffezzini M, Campodonico F, Capponi G, Manuputty E, Gerbi G. Fast-track surgery and technical nuances to reduce complications after radical cystectomy and intestinal urinary diversion with the modified Indiana pouch. *Surg Oncol* 2012;21(3):191-195.
- [28] Mosinska P, Zielinska M, Fichna J. Expression and physiology of opioid receptors in the gastrointestinal tract. *Curr Opin Endocrinol Diabetes Obes* 2016;23(1):3-10.
- [29] Nygren J, Thacker J, Carli F, Fearon KC, Norderval S, Lobo DN, Ljungqvist O, Soop M,

- Ramirez J, Enhanced Recovery After Surgery S. Guidelines for perioperative care in elective rectal/pelvic surgery: Enhanced Recovery After Surgery (ERAS(R)) Society recommendations. Clin Nutr 2012;31(6):801-816.
- [30] Rigg JR, Jamrozik K, Myles PS, Silbert BS, Peyton PJ, Parsons RW, Collins KS. Epidural anaesthesia and analgesia and outcome of major surgery: a randomised trial. Lancet 2002;359(9314):1276-1282.
- [31] Riley J, Eisenberg E, Muller-Schwefe G, Drewes AM, Arendt-Nielsen L. Oxycodone: a review of its use in the management of pain. Curr Med Res Opin 2008;24(1):175-192.
- [32] Roth B, Birkhauser FD, Zehnder P, Burkhard FC, Thalmann GN, Studer UE. Readaptation of the peritoneum following extended pelvic lymphadenectomy and cystectomy has a significant beneficial impact on early postoperative recovery and complications: results of a prospective randomized trial. Eur Urol 2011;59(2):204-210.
- [33] Scott MJ, Baldini G, Fearon KC, Feldheiser A, Feldman LS, Gan TJ, Ljungqvist O, Lobo DN, Rockall TA, Schricker T, Carli F. Enhanced Recovery After Surgery (ERAS) for gastrointestinal surgery, part 1: pathophysiological considerations. Acta Anaesthesiol Scand 2015;59(10):1212-1231.
- [34] Shabsigh A, Korets R, Vora KC, Brooks CM, Cronin AM, Savage C, Raj G, Bochner BH, Dalbagni G, Herr HW, Donat SM. Defining early morbidity of radical cystectomy for patients with bladder cancer using a standardized reporting methodology. Eur Urol 2009;55(1):164-174.

- [35] Smith K, Hopp M, Mundin G, Bond S, Bailey P, Woodward J, Palaniappan K, Church A, Limb M, Connor A. Naloxone as part of a prolonged release oxycodone/naloxone combination reduces oxycodone-induced slowing of gastrointestinal transit in healthy volunteers. *Expert Opin Investig Drugs* 2011;20(4):427-439.
- [36] Smith K, Hopp M, Mundin G, Leyendecker P, Bailey P, Grothe B, Uhl R, Reimer K. Single- and multiple-dose pharmacokinetic evaluation of oxycodone and naloxone in an opioid agonist/antagonist prolonged-release combination in healthy adult volunteers. *Clin Ther* 2008;30(11):2051-2068.
- [37] Sobczak M, Salaga M, Storr MA, Fichna J. Physiology, signaling, and pharmacology of opioid receptors and their ligands in the gastrointestinal tract: current concepts and future perspectives. *J Gastroenterol* 2014;49(1):24-45.
- [38] Staahl C, Christrup LL, Andersen SD, Arendt-Nielsen L, Drewes AM. A comparative study of oxycodone and morphine in a multi-modal, tissue-differentiated experimental pain model. *Pain* 2006;123(1-2):28-36.
- [39] von Hosslin T, Imboden P, Luthi A, Rozanski MJ, Schnider TW, Filipovic M. Adverse events of postoperative thoracic epidural analgesia: A retrospective analysis of 7273 cases in a tertiary care teaching hospital. *Eur J Anaesthesiol* 2016;33(10):708-714.
- [40] Vondrackova D, Leyendecker P, Meissner W, Hopp M, Szombati I, Hermanns K, Ruckes C, Weber S, Grothe B, Fleischer W, Reimer K. Analgesic efficacy and safety of oxycodone in combination with naloxone as prolonged release tablets in patients with moderate to

severe chronic pain. *J Pain* 2008;9(12):1144-1154.

- [41] Walder B, Schafer M, Henzi I, Tramer MR. Efficacy and safety of patient-controlled opioid analgesia for acute postoperative pain. A quantitative systematic review. *Acta Anaesthesiol Scand* 2001;45(7):795-804.
- [42] Winer AG, Sfakianos JP, Puttanniah VG, Bochner BH. Comparison of perioperative outcomes for epidural versus intravenous patient-controlled analgesia after radical cystectomy. *Reg Anesth Pain Med* 2015;40(3):239-244.

Figure legends:

Figure 1: CONSORT flow diagram:

Figure 2: Duration of TEA: Data presented as box plots with horizontal bars designating the median values, the vertical bars the 10th and 90th percentiles, and the open circles the extreme values. No significant differences between the 3 groups.

Figure 3: Pain scores with NRS scale mean value per day at rest (A) and during mobilization (B) per day according to the groups. No significant differences between the 3 groups at any time point. Data presented as box plots with horizontal bars designating the median values, the vertical bars the 10th and 90th percentiles, and the open circles the extreme values.

Table 1: Baseline characteristics

			Placebo	Oxycodone/ naloxone	Oxycodone	Overall
Gender	female	n/total (%)	11/30 (37%)	10/30 (33%)	10/30 (33%)	31/90 (34%)
	male	n/total (%)	19/30 (63%)	20/30 (67%)	20/30 (67%)	59/90 (66%)
ASA	2	n/total (%)	10/30 (33%)	18/30 (60%)	12/30 (40%)	40/90 (44%)
	3	n/total (%)	18/30 (60%)	8/30 (27%)	18/30 (60%)	44/90 (49%)
	4	n/total (%)	2/30 (7%)	4/30 (13%)	0/30 (0%)	6/90 (7%)
	mean (SD)		2.73 (± 0.58)	2.53 (± 0.73)	2.6 (± 0.5)	2.62 (± 0.61)
				66.03	68.47	67.17
Age [Years]	mean (SD)		67 (± 15.25)	(± 12.19)	(± 11.47)	(± 12.96)
					79.25	
Weight [kg]	mean (SD)		74.31 (± 18.9)	77.6 (± 15.36)	(± 15.15)	77.05 (± 16.5)
				168.93	171.07	
Height [cm]	mean (SD)		168.63 (± 9)	(± 7.88)	(± 9.26)	169.55 (± 8.7)
BMI	mean (SD)		25.84 (± 4.76)	27.15 (± 5.12)	27.08 (± 4.68)	26.69 (± 4.84)
			18.67		14.43	16.17
Smoking [Pack Years]	mean (SD)		(± 26.49)	15.4 (± 22.54)	(± 25.17)	(± 24.56)
Antihypertensive	n/total (%)		19/30 (63%)	16/30 (53%)	14/30 (47%)	49/90 (54%)
Beta-blocker	n/total (%)		5/30 (17%)	5/30 (17%)	7/30 (23%)	17/90 (19%)
Statin	n/total (%)		7/30 (23%)	8/30 (27%)	8/30 (27%)	23/90 (26%)
Aspirin	n/total (%)		9/30 (30%)	8/30 (27%)	3/30 (10%)	20/90 (22%)
Oral anti-diabetics	n/total (%)		6/30 (20%)	5/30 (17%)	6/30 (20%)	17/90 (19%)
Performed surgical intervention						
Orthotopic ileal bladder substitute						
	n/total (%)		9/30 (30%)	9/30 (30%)	10/30 (33%)	28/90 (31%)
Ileal conduit						
	n/total (%)		19/30 (63%)	12/30 (40%)	19/30 (63%)	50/90 (56%)
Continent catheterizable ileal reservoir						
	n/total (%)		1/30 (3%)	7/30 (23%)	1/30 (3%)	9/90 (10%)

Other	n/total (%)	1/30 (3%)	2/30 (7%)	0/30 (0%)	3/90 (3%)
Intraoperative fentanyl		394.2	341.7	415 (±191.8)	383.6
(µg)	mean (SD)	(±172.4)	(±230.1)		(±199.7)
Epidural rate (mL/h)	mean (SD)	6.7 (±1.73)	6.72 (±1.75)	7.47 (±0.9)	6.97 (±1.53)

Abbreviations: ASA = American Society of Anesthesiologists classification; BMI = body mass index; n = number of patients; SD = standard deviation

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Table 2: Difference (diff) in bolus administration, total epidural mixture administered per day, epidural mixture rate and rescue medication between postoperative day (POD) 3 (after having started the allocated drug) versus POD 4 and POD 5. Data presented as mean differences, standard deviation (\pm SD) and *P*-value.

	POD 3 vs 4 diff (\pm SD) <i>p</i>	POD 3 vs 5 diff (\pm SD) <i>p</i>	POD 4 vs 5 diff (\pm SD) <i>p</i>
Total epidural mixture rate (mL/d)			
	-22.9 (\pm 90.94)	-74.45 (\pm 98.08)	-47.59 (\pm 97.44)
oxycodone/naloxone	0.19	<0.01	0.01
	-31.41 (\pm 86.46)	-81.1 (\pm 90.29)	-50.97 (\pm 100.31)
oxycodone	0.06	<0.01	0.01
	-17.17 (\pm 95.02)	-53.24 (\pm 102.84)	-33.14 (\pm 105.67)
placebo	0.34	0.01	0.1
Epidural mixture rate (mL/h)			
oxycodone/naloxone	-1.41 (\pm 3.46) 0.04	-3.17 (\pm 3.68) <0.01	-1.69 (\pm 3.76) 0.02
	-2.17 (\pm 3.68)		
oxycodone	<0.01	-3.55 (\pm 3.58) <0.01	-1.31 (\pm 3.85) 0.08
placebo	-1.16 (\pm 4.09) 0.14	-2.79 (\pm 3.94) <0.01	-1.53 (\pm 3.98) 0.05
Rescue analgesia (morphine equivalent)			
oxycodone/naloxone	0.61 (\pm 1.39) 0.03	0.44 (\pm 1.31) 0.08	-0.12 (\pm 2.03) 0.76
oxycodone	-0.2 (\pm 1.07) 0.32	-0.26 (\pm 0.91) 0.14	-0.06 (\pm 0.69) 0.66
placebo	0.43 (\pm 2.91) 0.43	0.63 (\pm 3.43) 0.33	0.26 (\pm 4.01) 0.73

Figure 1:

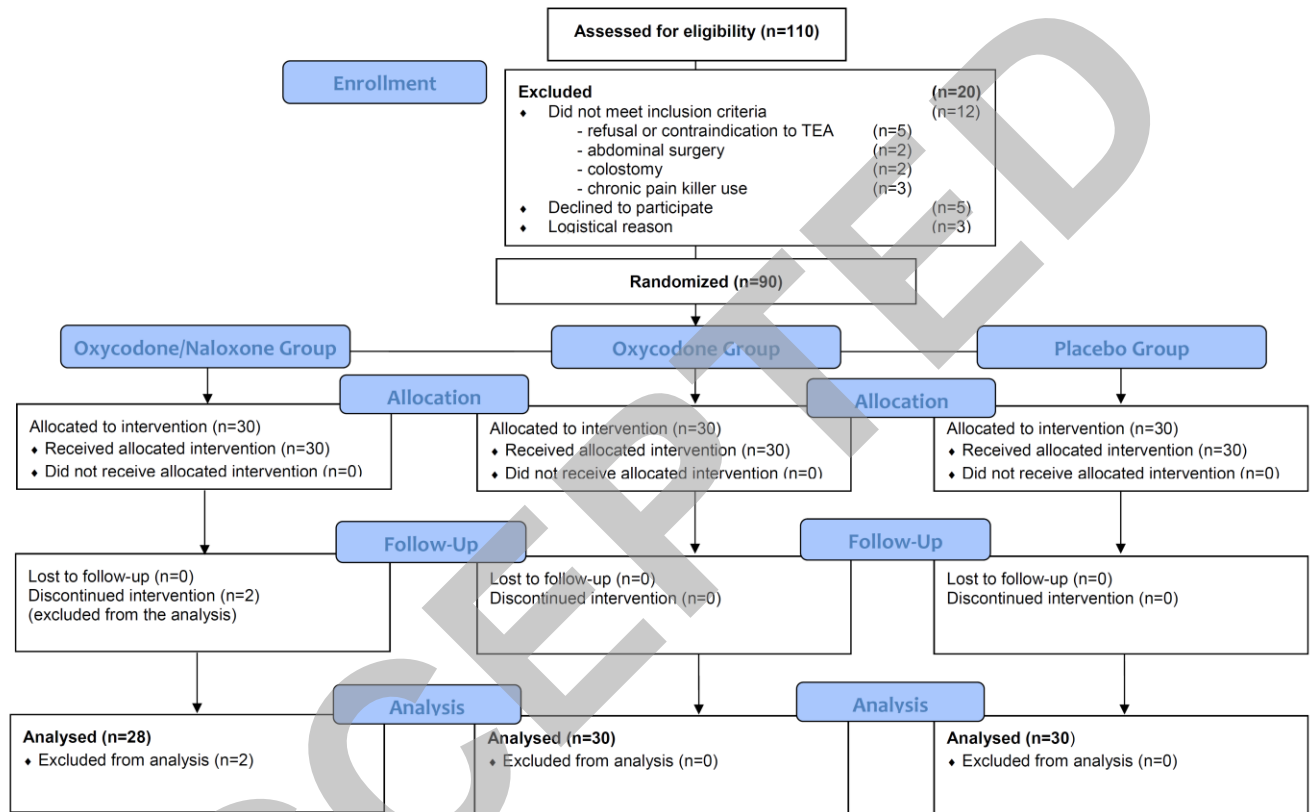


Figure 2

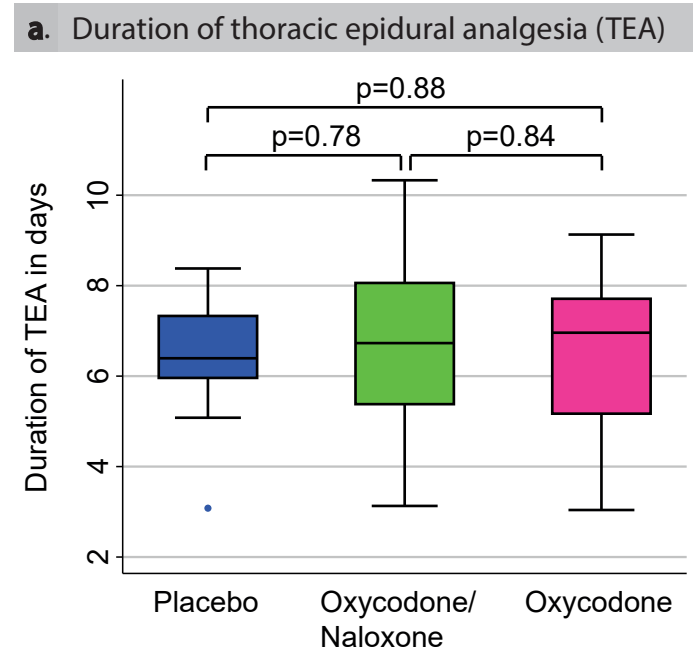


Figure 3

